Remarks

Introduction

The above-identified application has been carefully reviewed in light of the Office Action mailed October 18, 2004, which included a final rejection of the pending claims. A response to the Final Office Action is due January 18, 2005. Applicant submits that the amendments and remarks included herein show the present claims to be allowable and do not raise new issues. Therefore, applicant respectfully requests that this amendment be entered.

Claims 1-16 were pending, and claims 7 and 10 have been withdrawn from consideration. By way of this response, claims 1, 8, and 16 have been amended. Support for the amendments to the claims can be found in the application as originally filed, and no new matter has been added. Accordingly, claims 1-16 remain pending.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-6, 8, 9, and 11-16 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the specification to enable a person of ordinary skill in the art to make or use the invention.

Applicant respectfully disagrees and traverses the rejection as it relates to the present claims.

In that regard, the Office Action acknowledges that the examples disclose conjugates in ophthalmic compositions (e.g., ophthalmic drops). (Office Action, page 3, last paragraph). Thus, applicant concludes that the Examiner agrees that ophthalmically useful conjugates, such as conjugates useful in ophthalmic compositions, are enabled.

The present claims have been amended to make more clear that the present conjugates are ophthalmically useful and are effective when topically administered to the eye. As acknowledged in the Office Action, ophthalmic compositions which contain ophthalmically useful conjugates are enabled and described, at least as set forth in the examples.

In view of the above, applicant submits that the present claims, and claims 1-6, 8, 9, and 11-16 in particular, are sufficiently enabled to comply with 35 U.S.C. § 112, first paragraph, and respectfully requests that the rejection of the present claims based on this statutory provision be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claim 8 remains rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite for reciting the word "derivatives"

Claim 8 has been amended as set forth above to delete reference to "derivatives". Therefore, applicant submits that the rejection of claim 8 is moot.

Rejections Under 35 U.S.C. § 103

Claims 1-6, 8, 9, 11-13, 15, and 16 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Desantis Jr. (U.S. 2001/0047012; hereinafter Desantis) and Collins et al. (WO 01/92288; hereinafter Collins).

Applicant respectfully disagrees and traverses the rejection.

Among other things, applicant maintains that the Examiner has not met the burden of proof to establish a *prima facie* case of obviousness. The Office Action still fails to indicate where in the prior art, a suggestion or motivation is provided to modify or combine the teachings of Desantis or Collins to obtain the claimed conjugates. Absent such an indication, applicant submits that the rejections under 35 U.S.C. § 103 cannot be properly maintained. The motivation or suggestion to support a rejection under 35 U.S.C. § 103 must be clear and particular (*In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999); emphasis added), and "particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed" (*In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000)).

Applicant maintains that the prior art fails to provide a clear and particular showing that one of ordinary skill in the art would have been motivated to modify or combine the teachings of Desantis or Collins to obtain the claimed conjugates.

Desantis does not disclose, teach, or suggest the present invention. For example, Desantis does not disclose, teach, or even suggest a conjugate of any type, let alone, a conjugate of a therapeutic component and an efficacy enhancing component, as recited in the present claims.

In direct contrast to the present conjugates, Desantis discloses that separate compounds are separately administered to a patient. Further, Desantis discloses that at least one of the compounds is administered orally (see paragraph 0019). In addition, Desantis discloses a method of treating a person comprises administering at least one glutamate antagonist systemically, and at least one IOP-lowering composition topically to an affected eye (see paragraph 0032).

It is clear from the disclosure of Desantis that the glutamate antagonist and IOP-lowering agent are separate from each other and are administered in separate compositions and by separate routes. Because the glutamate antagonist and the IOP-lowering agent are separate and in separate compositions, and are administered by separate routes, the glutamate antagonist and the IOP-lowering agent cannot form a conjugate. In view of the separate agents in separate compositions administered by separate routes taught by Desantis, applicant submits that Desantis actually teaches away from pharmaceutical conjugates of any kind, and in particular the conjugates recited in the present claims. "As a general rule, references that teach away cannot serve to create a prima facie case of obviousness." (*McGinley v. Franklin Sports, Inc.* CAFC 8/21/01 citing *In re Gurley*, 31 USPQ2d 1131, (Fed. Cir. 1994)). Thus, applicant submits that a person of ordinary skill in the art would not be

motivated to modify Desantis or combine Desantis with Collins for the purpose of making obvious the presently claimed conjugates.

In addition, even if Desantis were to be erroneously combined with Collins, the combination does not disclose, teach, or suggest all of the elements recited in the present claims.

For example, Collins discloses a conjugate of an antibiotic, such as amantadine HCl, and a transcobalamin- or intrinsic factor-binding agent (TC- or IF-binding agent, respectively). The TC- or IF-binding agent is an agent that binds to a vitamin B_{12} transport protein. Thus, Collins discloses that amantadine HCl is one of many potential therapeutic agents, that may be coupled to a TC- or IF-binding agent.

Collins does not disclose, teach, or suggest the present invention. For example, Collins does not disclose, teach, or even suggest a conjugate comprising an efficacy enhancing component having the chemical formula A recited in the present claims. As discussed above, the amantadine HCl disclosed by Collins is a therapeutic component, not an efficacy enhancing component. In addition, Collins does not disclose, teach, or even suggest why a person of ordinary skill in the art might choose amantadine HCl from the lengthy list of potential antibiotics to couple to the TC- or IF-binding agent.

Moreover, the TC- or IF-binding agent disclosed by Collins has a completely different and distinct chemical structure than the efficacy enhancing component recited in the present claims.

The chemical structure of the TC- or IF-binding agent is shown at page 39 of Collins. Thus, the TC- or IF-binding agent disclosed by Collins and the efficacy enhancing component recited in the present claims are both structurally and functionally different and distinct, one from the other.

Therefore, even if Collins were to be erroneously combined with Desantis, the combination would fail to disclose, teach, or even suggest a conjugate which includes an efficacy enhancing component having the chemical formula A, as recited in the present claims.

The Office Action states that 1-Aminoadamantane analogues such as memantine are established in the prior art as useful agents for conjugation with poorly soluble drugs. However, the Office Action fails to identify a prior art reference to support such a position.

As discussed above, Collins discloses amantadine HCl as one of many potential therapeutic components, and does not teach that amantidine HCl is useful in conjugation with poorly soluble drugs. In fact, Collins discloses that amantadine HCl is only one of more than 100 different potential antibiotic agents that may be conjugated to the TC- or IF-binding agent. Moreover, Collins discloses that the amantadine HCl is the agent that is poorly soluble and may benefit from conjugation to the TC- or IF-binding agent.

The mention of amantadine HCl identified by the Examiner at page 92 of Collins relates to one of more than 100 different

antibiotic agents that may be conjugated to the TC- or IF-binding agent disclosed by Collins.

Applicant submits that the prior art fails to provide a clear and particular showing that one of ordinary skill in the art would have been motivated to combine the deficient teachings of Desantis and Collins, let alone to combine them and obtain the claimed conjugates.

Applicant submits that the listing of many different antibiotic agents of Collins provides no more than speculation of potential types of therapeutic agents that can be used in the conjugates of Collins. The listing does not provide any motivation or incentive to a person of ordinary skill in the art to combine Desantis and Collins, let alone to combine Desantis and Collins and select amantadine HCl as an efficacy enhancing component and to form a conjugate with a different therapeutic component, as recited in the present claims.

Applicant submits that, based on the teachings of Desantis and Collins, alone or in any combination, a person of ordinary skill in the art would still be required to guess, test, speculate, and/or arbitrarily "pick and choose" a specific antibiotic agent (e.g., amantadine HCl) from among the long list of different antibiotic agents identified by Collins, let alone to do so and further to use that amantadine HCl as an efficacy enhancing component and couple it to a therapeutic component, as recited in the present claims. Collins does not place any significance whatsoever in the types of antibiotic agents relative to the other agents disclosed, and Collins does not disclose, teach, or even suggest that the amantadine HCl

provides any efficacy enhancing capabilities whatsoever. As discussed above, Collins specifically discloses that the amantadine HCl is a therapeutic component. Thus, at best, even if Desantis and Collins could be erroneously combined, the combination would result in two therapeutic components, not a conjugate comprising a therapeutic component and an efficacy enhancing component, as recited in the present claims.

Simply put, the brief mention in Collins of amantadine HCl in a long list of other, different antibiotic agents, is insufficient for Collins, alone or in any combination with Desantis, to teach or even suggest the conjugates recited in the presently rejected claims. For example, the brief mention of amantadine HCl is insufficient for Collins, alone, or in combination with Desantis, to teach or even suggest an ophthalmic conjugate comprising an ophthalmically useful therapeutic component coupled to an efficacy enhancing component having the formula A, as recited in the present claims.

Given the teachings of Collins without applicant's invention and disclosure, applicant submits that even if a person of ordinary skill in the art would choose amantadine HCl from the lengthy list of other antibiotic agents, that person would use the amantadine HCl as a therapeutic agent based on the teachings of either or both of Collins and Desantis. Only after knowing of applicant's invention and disclosure would one of ordinary skill in the art select amantadine HCl from among the many other different antibiotic agents disclosed by Collins, and use such amantadine HCl as an efficacy enhancing component, as recited in the present claims. Applicant submits that such hindsight is an improper basis for rejecting patent claims.

In view of the above, applicant submits that the present claims, and claims 1-6, 8, 9, 11-13, 15, and 16 in particular, are unobvious from and patentable over Desantis or Collins, taken alone or in any combination, under 35 U.S.C. § 103.

In addition, each of the present dependent claims is separately patentable over the prior art. For example, none of the prior art disclose, teach, or even suggest the present conjugates including the additional feature or features recited in any of the present dependent claims. Therefore, applicant submits that each of the present claims is separately patentable over the prior art.

Conclusion

In conclusion, applicant has shown that the present claims satisfy the requirements of 35 U.S.C. § 112, and are not anticipated by and are unobvious from and patentable over the prior art under 35 U.S.C. §§ 102 and 103. Therefore, applicant submits that the present claims, that is claims 1-16 are allowable. Therefore, applicant respectfully requests the Examiner to pass the above-identified application to issuance at an early date. Should any matters remain unresolved, the Examiner is requested to call (collect) applicant's attorney at the telephone number given below.

Respectfully submitted,

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